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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/544,910	04/07/00	HUANG Y	06510/121US1

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 01/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examin r	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 4, 2000 and January 5, 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 and 5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The Election of Group I, claims 1-11, in Paper No. 6 filed on December 4, 2000 are acknowledged and have been entered. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The Election of antibodies as a species for examination in Paper No. 8 filed on January 5, 2001 is acknowledged and has been entered.

3. Claims 1-35 are pending in the application. Claims 12-35 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to nonelected inventions. Claims 1-11 are currently under prosecution.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for reducing the level of triglyceride and at least one very-low-density-lipoprotein (VLDL) in the plasma of a host and to a method of treating a host suffering from a disease condition associated with elevated levels of tryglyceride and at least one VLDL, said methods comprising administering to said host an effective amount of an agent that reduces the amount of biologically active apolipoprotein E (apoE) in the plasma of said host.

As broadly written, the claims are drawn to a method of treatment wherein *any* agent that causes a reduction in the amount of biologically active apoE in the plasma of a mammal, and thereby reduces the level of triglyceride and at least one VLDL in said plasma, can be administered to the mammal; although it is noted that the identity of said agent is undisclosed. It is further noted that the claims encompass a method for the treatment of humans with this undisclosed agent, wherein said human has a disease condition associated with elevated levels of triglyceride and at least one VLDL in the plasma, such as hyperlipidemia. Support for these broad interpretations of the claims appear in the specification on page 19, lines 6-11.

In this case, the written description only sets forth a catalog of various generic types of agents that may possibly meet the requirements of the claims and would be generally considered for use in the claimed method by one of skill in the art because of their putative potential to mediate the desired effects. For example, the specification teaches that the agent may be an "apoE inhibitor" (page 10, line 2). Further, the specification teaches that "the apoE inhibitor may be a number of different types of agents, such as small molecules, antibodies or binding fragments thereof, and the like" (page 10, lines 5-6). The specification also teaches that "agents are also found among biomolecules, including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof" (page 10, lines 15-17). Then, on page 14, the specification teaches that antisense nucleic acid molecules are contemplated for use as agents in practicing the claimed invention (line 11). Finally, on page 16, lines 8-9, the specification teaches that catalytic nucleic acids molecules, such as ribozymes, could be used as agents.

In the response to the Office Action mailed on October 10, 2000 Applicant made an election of the species: antibodies. However, it is noted that Applicant does not distinctly and specifically point out, either in the claims or in the specification the identity of even one antibody suitable for use as an agent in practicing the invention as claimed. While it is generally known in the art that there are antibodies that are indeed capable of blocking or neutralizing the activities of an antigen (for example, in the instant case, an anti-apoE antibody might be capable of blocking the interaction between apoE and the LDL receptor), one of skill in the art also

knows that there are numerous examples of antibodies capable of specific interaction with apoE, in this instance that will not block its interaction with the LDL receptor. Accordingly, one of skill in the art cannot predict which antibodies, if any will be suitably provide efficacy in practicing the claimed invention. The specification does not teach the antigenic specificity required of an agent antibody to be used in the claimed method; therefore, the species of agent antibodies is also generic. Nonetheless, even if Applicant were to have contemplated the use of an anti-apoE antibody as an agent, clearly not all anti-apoE antibodies will be capable of being used effectively in the method.

Moreover, it is noted that each of the putative therapeutic agents cataloged in the specification in the generic sense (i.e. antisense oligonucleotides, antibodies, ribozymes, etc.), which could possibly be used to mediate the desired effect of a reduction in the level of apoE in the plasma of a mammal, would have been contemplated for use by one of skill in the art. Each member of the genus of putative agents is commonly known in the art to have been generally used to effect reductions in the activity and/or expression level of a targeted molecule. For example, while not always practical, in theory, one could design an antisense oligonucleotide to inhibit the expression of any gene, provided that the nucleotide sequence of the gene is known. Thus, there is no apparent contribution to the art in regard to the specific agent that is to be used in practicing the claimed invention.

Again, the specification is silent as to the actual identity of any one agent that would be ably used in practicing the claimed invention. This

disclosure of a catalog of potentially effective agents is deemed insufficient because it cannot be predicted by one of skill in the art that such an agent actually exists, or could be created that would fulfill the requirements of the claims. The specification is devoid of exemplification of the claimed method and of specific teachings that would enable one of skill in the art to practice the claimed invention; thus, it would seem that Applicant did not actually possess an agent at the time of filing which could be used to practice the invention as claimed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Moreover, although drawn to the nucleic acid art, the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant invention. In *Fiers v. Revel* and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.* the court found that adequate written description requires more than a mere statement that it (a nucleic acid) is part of the invention. The nucleic acid itself is required; or in the instant case, an

example of an agent that has the prescribed effects and a showing by exemplification of its utility in practicing the claimed invention is required.

Furthermore, although again drawn to the nucleic acid art, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Accordingly, there is an inference that an adequate description of an agent also requires a very precise definition, including an indication of chemical identity of said agent and the quantity of said agent that would be therapeutically effective. There is also an inference that the mere description of a genus of generically applicable agents, limited only by a disclosed generic statement relating the functional activities of the species, does not provide such an adequate written description of the genus.

As set forth above, Applicant contemplates many distinct compounds for use as agents in practicing the claimed invention. However, no disclosure, beyond the mere mention of these potentially effective agents, which putatively could reduce the amount of triglyceride and at least one

VLDL in the plasma of a mammal, is made in the specification. Moreover, there is insufficient guidance in the specification so as to enable one of skill in the art to practice the claimed invention. There is merely an inference in the specification that one of skill in the art could use one of the provided animal models to test and identify putatively effective agents. Additionally, one of skill in the art would necessarily have to establish what amount of the selected agent would provide efficacy since the specification only teaches that "dose levels can vary as a function of the specific compound" (page 16, line 21). As such, the Applicant merely appears to extend an invitation to those skilled in the art to discover which, if any members of the genus of agents could be used efficaciously in practicing the claimed invention. Because the efficacy and applicability of the genus of agents is highly variant and because one of skill in the art would not have a reasonable expectation of success in practicing the invention as claimed without first testing an agent, the disclosure of a list of putatively effective agents that could be tested for utility in practicing the claimed invention and a general teaching of the definition of the required biological effect of said agent is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

7. Claims 1, 3-8, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for reducing the level of triglyceride and at least one very-low-density-lipoprotein (VLDL) in the plasma of a host and to a method of treating a host suffering from a disease condition associated with elevated levels of tryglyceride and at least one VLDL, said methods comprising administering to said host an effective amount of an agent that reduces the amount of biologically active apolipoprotein E (apoE) in the plasma of said host.

It is noted that as broadly written, the claims are drawn to a method of treatment wherein *any* agent that causes a reduction in the amount of biologically active apoE in the plasma of a mammal, and thereby reduces the level of triglyceride and at least one VLDL in said plasma, can be administered to the mammal; although it is noted that the identity of said agent is undisclosed. It is further noted that the claims encompass a method for the treatment of humans with this undisclosed agent, wherein said human has a disease condition associated with elevated levels of triglyceride and at least one VLDL in the plasma, such as hyperlipidemia. Support for these broad interpretations of the claims appear in the specification on page 19, lines 6-11.

The specification teaches as set forth in the 35 USC § 112, first paragraph rejection above and also teaches general methods of formulating agents for pharmaceutical use, and general methods for administering these pharmaceutical compositions to host mammals, including humans (see pages 17-20). The specification teaches that there

is a correlation between the level of apoE in the plasma of a mammal the level of triglyceride and VLDL in the plasma of a mammal (page 34, lines 2-5).

In general, the teachings of the specification cannot be extrapolated to the enablement of the claims because the specification provides insufficient guidance and exemplification of the use of the claimed method to effectively reduce the plasma level of triglyceride and at least one VLDL in the plasma of a mammal and to thereby treat hyperlipidemia in said mammal. It is noted that, according to the limitations of both claims 1 and 5, the agent to be administered to a mammal must reduce the amount of active apoE in the plasma of said mammal. However, as stated above, the specification does not identify a specific agent that could be formulated for use in practicing the claimed invention. The specification does not exemplify the method and there is no teaching that such an agent, one which is capable of mediating the desired effects, including a reduction in the level of plasma active apoE, actually exists. Moreover, the specification is deficient in identifying an agent capable of reducing the level of apoE3, per se, in the plasma of a host; it is noted that this limitation, appearing claims 4 and 11, would require one to identify an allele-specific inhibitory agent to practice the invention as claimed, unless an agent that inhibits or reduces the expression of all apoE alleles is suitable. Also in regard to the limitations of claims 4 and 11, the specification provides no guidance as to how patients are to be selected. However, the claim limitations clearly require that said patients express at least one apoE3 allele; otherwise, there would not be a reasonable expectation of successfully practicing the

invention. The specification provides no guidelines for selecting against patients that do not meet the requirements of the claims, for that matter. Moreover, the specification does not teach how the efficacy of the method of treatment can be measured or determined and provides insufficient guidance in these methods, by which the claimed effects are to be recognized, categorized, analyzed, or interpreted.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

One of skill in the art cannot predict that the claimed method of treatment will be effective, particularly since the specification has not set forth an agent that has been shown to be capable of mediating the effects required by the claims. It is well known that the art of drug discovery for therapy is highly unpredictable. For example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs).

Although drawn to the identification and development of agents and methods for treatment of cancer, the cautionary note of the above reference applies equally well to the art of identifying and developing a pharmaceutical agent for treatment of hyperlipidemia. It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of any agent capable of reducing the amount of active apoE in the plasma of a host would function as claimed based only upon an implied and/or predicted mechanism of action alone.

In addition, pharmaceutical agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the targeted tissue(s) and interact at the proper site, and they must do so at a sufficient concentration and for a sufficient period of time so as to be effective. In addition, variables such as biological stability, half-life, and clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation, or due to an inherently short half-life. The composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted. Alternatively, the composition may be absorbed by fluids, cells and tissues where the formulation has no effect and circulation into the target area may be insufficient to carry the composition and to permit a large enough local concentration to be established.

Again, it is noted that Applicant elected the species of agent: antibodies. However, as set forth in the 35 USC § 112, first paragraph

rejection above, one skilled in the art cannot predict that an antibody capable of specific binding to apoE will inhibit the activity of apoE since it is well known in the art that not all antibodies directed against either a receptor or ligand are neutralizing, that is capable of blocking the interaction between the receptor and its ligand.

While some antibodies directed against apoE are, indeed, capable of inhibiting the biological function of apoE by, for example, blocking the binding of apoE to the LDL receptor, generally, the skilled practitioner in the art would not contemplate the use of an antibody to reduce the expression of apoE, in order to effect a reduction in the level of VLDL and triglyceride in the serum of a subject. Rather, one skilled in the art might contemplate the use of antisense therapy to reduce the expression level of apoE, which in turn would, of course, reduce the amount of plasma active apoE in a host. In fact, it is clear that Applicant also contemplates antisense therapy for treatment of hyperlipidemia. Support for the use of an antisense oligonucleotide as an agent in the claimed invention appears in the specification on page 14, line 12 to page 16, line 16, where general recitations of the preparation and use of antisense oligonucleotides are made.

As drawn specifically the use of antisense oligonucleotides as an agent in the claimed method, one cannot extrapolate the teachings of the specification to the enablement of the claims because the specification does not enable one of skill in the art to use any antisense oligonucleotide targeted to the transcript encoding the apoE3 allele specifically, or for that matter, any transcript encoding any apoE. One of skill in the art could

make oligonucleotides targeting any region of the transcripts; however, because of the unpredictability in the success of using antisense oligonucleotides, one would be forced into undue experimentation to practice the invention as claimed. Actually, picking and choosing the target region for the oligonucleotide has proven to be cumbersome because of the unpredictable nature of the oligonucleotide's binding, specificity, and/or ability to inhibit translation of the transcript. James, et *al (Antiviral Chemistry and Chemotherapy* **2**: 191-214, 1991) teaches on page 198:

> The results seem to suggest that whether a target sequence is susceptible to antisense RNA has little to do with whether or not it contains the primary sequence features, such as splice sites, cap sites, initiation or termination codons that we would imagine to be important targets. This point is demonstrated in studies in which one member of a nested set of antisense RNA is poorly inhibitory while a smaller one, completely included within the former, is strongly inhibitory.
>
> It is clear that an investigation of the primary structure of an antisense RNA cannot predict whether or not is shall inhibit expression.

Even more recently, Roush, et al (*Science* **276**: 1192-1193, 1997) teaches that "for some reason, antisense oligos gives random results, and when it works it's luck" and also teaches that companies have "found success by sifting through dozens of oligos that complement slightly different segments of the targeted mRNA, and selecting those that work" (page 1193, column 1). Consequently, as drawn even to antisense oligonucleotides, one can imagine that the claims encompass many non-working embodiments. As such, finding the working embodiments among

the possibilities would require undue experimentation. In regard to other types of agents encompassed by the claims, one would be equally challenged to identify agents that fulfill the requirements of the claims.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because in claims 1 and 5 there is no positive process step that clearly relates back to the preamble of the claims. Amending the last line of claims 1 and 5 to recite the phrases "whereby the level of triglyceride and at least one VLDL in the plasma of said host is reduced" and "whereby said host is treated", respectively, can obviate the rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Ditschuneit, et al (*Journal of International Medical Research* **20**: 197-210, 1992), as evidenced by Pedreno, et al (*Metabolism: Clinical and Experimental* **49**: 942-949, 2000) and Durington, et al (*Artherosclerosis* **138**: 217-225, 1998).

Claims 1-4 are drawn to a method for reducing the plasma level of at least one of VLDL and triglycerides in a host, said method comprising administering to said host an effective amount of an agent which at least reduces the amount of plasma active apoE in said host (claim 1), wherein said agent inhibits apoE (claim 2), or wherein said agent reduces the expression of apoE (claim 3), or wherein said apoE is apoE3 (claim 4). Claims 5-11 are drawn to a method of treating a host suffering from a disease associated with elevated plasma levels of at least one of VLDL and triglycerides, said method comprising administering to said host an effective amount of an agent that at least reduces the plasma amount of active apoE in said host (claim 5), wherein said disease condition is a hyperlipidemia (claim 6) wherein said hyperlipidemia is either Type IV or Type IIb hyperlipidemia (claims 7 and 8, respectively), or wherein said agent inhibits apoE (claim 9) or reduces the expression of said apoE (claim 10), or wherein said apoE is apoE3 (claim 11).

The prior art reference, Ditschuneit, et al, teaches a method of treating female patients with hyperlipoproteinaemia type IV (i.e. Type IV hyperlipidemia) with an agent, gemfibrozil. The reference teaches that the effect of said treatment is a reduction in the concentrations (i.e. amount) of triglyceride and very-low-density-lipoprotein (VLDL) in the serum (i.e. blood plasma, without the clots); see abstract.

The mechanism by which an agent acts to treat a disease, that is the mechanism by which said agent causes a therapeutically desired effect is an inherent property of that agent. As set forth above, gemfibrozil, the agent used in the method of Pedreno, et al to treat patients with Type IV hyperlipidemia, causes a reduction in the level of triglyceride and VLDL in the plasma of a mammal. A further known property of gemfibrozil is that the agent causes a reduction in the level of apoE, as evidenced by the teachings of Pedreno, et al. Specifically, the evidentiary reference, Pedreno, et al teaches that treatment of patients having familial hypertriglyceridemia (i.e. Type IV hyperlipidemia) by gemfibrozil therapy results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients. Moreover, Pedreno, et al teach that gemfibrozil therapy results in a decrease in the apoE content of VLDL in the plasma of the patient (see abstract).

The specification teaches that "by active apoE is meant apoE that is able to function in its normal physiological role" (page 9, lines 21-22); it is known in the art that apoE functions normally by incorporation into VLDL. As set forth above, the evidentiary reference, Pedreno, et al, specifically teaches that it is an inherent property of gemfibrozil to cause a reduction in

the level of apoE incorporated into VLDL, and therefore to inhibits the normal function of apoE. Moreover, the Pedreno, et al teach that the actual level of apoE in the plasma of patients treated with gemfibrozil is decreased, indicating a reduction in the level of expression of apoE has occurred as a result of the treatment. Therefore, another inherent property of gemfibrozil is to cause a reduction in the level of expression of apoE, as evidenced by Pedreno, et al.

The prior art agent disclosed by Ditschuneit, et al is deemed to be the same as the agent of the instant claims, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or would not function identically in the claimed method of treatment wherein said product inhibits apoE and/or reduces the expression of apoE. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed agent is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

The method of the prior art disclosed by Ditschuneit, et al comprises the same method steps as claimed in the instant invention, that is treating Type IIb hyperlipidemia by administering an agent that at least reduces the plasma amount of active apoE3 in a host, thus the methods claimed in claims 4, 8, and 11 are anticipated because the method will inherently lead

to conferring a treatment of Type IIb hyperlipidemia in a patient by reducing the level of apoE3 in the patient. See Ex parte Novitski 26 USPQ 1389 (PTO Board of Patent Appeals and Interferences, 1993).

This assertion is supported by the evidentiary teachings of Durrington, et al. Durrington, et al teach that a method of treating patients with type IIb hyperlipoproteinaemia (i.e. type IIb hyperlipidemia) comprising administering to said patients gemfibrozil, an agent that causes a reduction in the serum (i.e. blood plasma, without the clots) concentration (i.e. amount) of triglyceride and very low density lipoprotein (VLDL); see abstract.

All the limitations of the claims have been met.

12. Claims 1, 3-8, and 10-11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Yoshino, et al (*Artherosclerosis* **75**: 67-72, 1989).

Claims 1, 3, and 4 are drawn to a method for reducing the plasma level of at least one of VLDL and triglycerides in a host, said method comprising administering to said host an effective amount of an agent which at least reduces the amount of plasma active apoE in said host (claim 1), wherein said agent reduces the expression of apoE (claim 3), or wherein said apoE is apoE3 (claim 4). Claims 5-8, 10, and 11 are drawn to a method of treating a host suffering from a disease associated with elevated plasma levels of at least one of VLDL and triglycerides, said method comprising administering to said host an effective amount of an agent that at least reduces the plasma amount of active apoE in said host

(claim 5), wherein said disease condition is a hyperlipidemia (claim 6) wherein said hyperlipidemia is either Type IV or Type IIb hyperlipidemia (claims 7 and 8, respectively), or wherein said agent reduces the expression of said apoE (claim 10), or wherein said apoE is apoE3 (claim 11).

Yoshino, et al that a method of treating patients having hyperlipoproteinaemia type IIb (i.e. Type IIb hyperlipidemia) comprising administering to said patients, pravastatin, an agent that reduces the level of apoE in the serum (i.e. plasma, without the clots) of the patient (abstract). Specifically, Yoshino, et al teach that treatment of patients having type IIb hyperlipidemia associated with non-insulin dependent diabetes by pravastatin therapy results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients (see abstract, Table 2, page 69, and Table 3, page 70). Thus, the prior art reference teaches that the actual level of apoE in the plasma of patients treated with pravastatin is decreased, indicating a reduction in the level of expression of apoE has occurred as a result of the treatment.

The prior art agent is deemed to be the same as the agent of the instant claims, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or would not function identically in the claimed method of treatment wherein said product inhibits apoE and/or reduces the expression of apoE. In the absence of evidence to the

contrary, the burden is upon the applicant to prove that the claimed agent is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

The method of the prior art comprises the same method steps as claimed in the instant invention, that is, treating Type IV hyperlipidemia by administering an agent that at least reduces the plasma amount of active apoE3 in a host, thus the methods claimed in claims 4, 7, and 11 are anticipated because the method will inherently lead to conferring a treatment of Type IV hyperlipidemia in a patient by reducing the level of apoE3 in the patient. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

All the limitations of the claims have been met.

13. Claims 1, 3-8, and 10-11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Connor, et al (*Annals of the New York Academy of Sciences* **683**: 16-34, 1993).

Claims 1, 3, and 4 are drawn to a method for reducing the plasma level of at least one of VLDL and triglycerides in a host, said method comprising administering to said host an effective amount of an agent which at least reduces the amount of plasma active apoE in said host (claim 1), wherein said agent reduces the expression of apoE (claim 3), or wherein said apoE is apoE3 (claim 4). Claims 5-8, 10, and 11 are drawn to a method of treating a host suffering from a disease associated with elevated plasma levels of at least one of VLDL and triglycerides, said

method comprising administering to said host an effective amount of an agent that at least reduces the plasma amount of active apoE in said host (claim 5), wherein said disease condition is a hyperlipidemia (claim 6) wherein said hyperlipidemia is either Type IV or Type IIb hyperlipidemia (claims 7 and 8, respectively), or wherein said agent reduces the expression of said apoE (claim 10), or wherein said apoE is apoE3 (claim 11).

Connor, et al teach a method of treating hypertriglyceridemic patients with type IIb combined hyperlipidemia and type IV hyperlipidemia comprising administering dietary n-3 fatty acids. Connor, et al teach a dramatic reduction in plasma triglycerides resulting from the treatment, as well as a decrease in the levels of VLDL and apoE (see abstract). Thus, the prior art reference teaches that the actual level of apoE in the plasma of patients treated with pravastatin is decreased, indicating a reduction in the level of expression of apoE has occurred as a result of the treatment.

The prior art agent is deemed to be the same as the agent of the instant claims, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or would not function identically in the claimed method of treatment wherein said product inhibits apoE and/or reduces the expression of apoE. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed agent is functionally different than that taught by the prior art and to establish

patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

The method of the prior art comprises the same method steps as claimed in the instant invention, that is, treating hyperlipidemia by administering an agent that at least reduces the plasma amount of active apoE3 in a host, thus the methods claimed in claims 4 and 11 are anticipated because the method will inherently lead to conferring a treatment of hyperlipidemia in a patient by reducing the level of apoE3 in the patient. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

All the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 2, 4-9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huff, et al (*Arteriosclerosis and Thrombosis* **11**: 221-233, 1991) in view of Huang, et al (*Journal of Biological Chemistry* **273**: 26388-26393, 1998).

Claims 1, 2, and 4 are drawn to a method for reducing the plasma level of at least one of VLDL and triglycerides in a host, said method comprising administering to said host an effective amount of an agent

which at least reduces the amount of plasma active apoE in said host (claim 1), wherein said agent inhibits apoE (claim 2), or wherein said apoE is apoE3 (claim 4). Claims 5-9 and 11 are drawn to a method of treating a host suffering from a disease associated with elevated plasma levels of at least one of VLDL and triglycerides, said method comprising administering to said host an effective amount of an agent that at least reduces the plasma amount of active apoE in said host (claim 5), wherein said disease condition is a hyperlipidemia (claim 6) wherein said hyperlipidemia is either Type IV or Type IIb hyperlipidemia (claims 7 and 8, respectively), or wherein said agent inhibits apoE (claim 9), or wherein said apoE is apoE3 (claim 11).

Huff, et al teach an anti-apoE monoclonal antibody, known to block the binding of apoE to the low-density-lipoprotein (LDL) receptor (see abstract). Huff, et al also suggest that apoE mediates the accumulation of cholesterol in the macrophages incubated in the presence of VLDL isolated from patients with type IV hyperlipoproteinemia.

Huff, et al do not teach a method of reducing the plasma level of at least one VLDL and triglycerides in a host nor do they teach a method of treating a host suffering from a disease condition associated with elevated levels of at least one VLDL and triglycerides, said methods comprising administering to said host an effective amount of an agent that at least reduces the amount of plasma active apoE3 in said host, wherein said agent inhibits apoE.

Huang, et al teach that overexpression and accumulation of apoE causes hypertriglyceridemia and also teach that animals with the disease have elevated levels of triglyceride and VLDL in the serum (see abstract).

It is noted that the specification teaches that hypertriglyceridemia is a broadly defined disease condition, wherein elevated levels of lipid, lipoprotein, and/or cholesterol occur in a patient, that includes both type IIb and type IV hyperlipidemia (see pages 1-2). It is further noted that the specification teaches on page 10, lines 1-6, that a suitable agent for use in practicing the claimed invention would be one that inhibits the normal function of apoE, rendering the molecule incapable of binding the LDL receptor; therefore, the prior art antibody falls within the scope of the claims in light of the specification.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the anti-apoE antibody of Huff, et al to treat patients suffering from a disease condition associated with elevated levels of triglyceride and VLDL, including type IIb and type IV hyperlipidemia, because the prior art antibody is known to block the binding of apoE to the LDL receptor and thus inhibits the normal function of apoE and because it would be desirable to reduce the activity of apoE in patients suffering from said conditions since Huang, et al teach that apoE is overexpressed and accumulates in these patients.

One would have been motivated to use the antibody of Huff, et al to treat patients with a disease associated with elevated levels of triglyceride and VLDL by reducing the amount of active apoE in the plasma of said patients, in order to reduce the level of triglyceride and VLDL in the blood

and prevent and/or minimize the development of atherosclerosis in the patients, because it is well known in the art that elevated levels of VLDL and triglyceride in the blood are associated with artherosclerosis and heart disease.

It is noted that the antibody of Huff, et al specifically binds apoE, but it is not disclosed that the antibody binds specifically to apoE3, encoding by a specific allele of the gene encoding apoE. It is expected that the antibody is not allele-specific and would be capable of specific binding to apoE3; that is, the prior art agent is deemed to be the same as the agent of the instant claims, absent a showing of any unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or would not function identically in the claimed method of treatment wherein said product inhibits apoE3. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed agent is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

Conclusions

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

CONNA WORTMAN
PRIMARY EXAMINER

slr
January 25, 2001